DEPARTMENT OF HEALTH & HUMAN SERVICES

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January 14, 2002

John S. T. Gallagher
President
North Shore University Hospital
300 Community Drive
Manhasset, New York 11030

RE: Human Research Subject Protections Under Multiple Project Assurance (MPA) M-1302

Dear Mr. Gallagher

The Office for Human Research Protections (OHRP) has reviewed North Shore-Long Island Jewish Health System's (NSLIJHS') December 11, 2001 report responding to allegations of noncompliance with Department of Health and Human Services (HHS) regulations for the protection of human subjects that were described in OHRP's November 6, 2001 letter.

The allegations involved the following:

(1) Human subject research involving a clinical trial of an intraocular lens was conducted on a subject without obtaining the legally effective informed consent of the subject, in contravention of the requirements of HHS regulations at 45 CFR 46.116.

(2) The subject was harmed by the research.

Based upon its review of NSLIJHS' report, OHRP finds no evidence to substantiate the above allegations. In particular, OHRP acknowledges NSLIJHS' report that (i) the intraocular lens implanted in the complainant was not investigational and was released for commercial distribution on April 9, 2001; (ii) the complainant was not treated as part of a clinical trial of a medical device when the intraocular lens was implanted.

As a result, there should be no need for further involvement of OHRP in this matter. Of course, OHRP must be notified should new information be identified which might alter this determination.
At this time, OHRP provides the following guidance regarding the NSLIJHS Institutional Review Board (IRB) Policies and Standard Operating Procedures:

(1) The policies and procedures should be expanded to include additional operational details about the following procedures:

(a) The procedures which the IRB will follow for reporting its findings and actions to the institution.

(b) The procedures which the IRB will follow for determining which projects need verification from sources other than the investigators that no material changes have occurred since previous IRB review.

(2) Regarding Section 2.3, page 22, the paragraph under the heading GUIDANCE, OHRP notes that a quorum of the IRB is defined as "greater than half of the voting membership." Please note that in accordance with the requirements of HHS regulations at 45 CFR 46.108(b), the definition of quorum should be revised to include at least one member whose primary concerns are in nonscientific areas.

(3) Regarding the procedure for initial review of research by the convened IRB on page 22, OHRP notes that a primary reviewer system is used for initial review of research and that under this system, all IRB members receive a copy of a protocol summary.

On page 27, OHRP notes reference to "IRB Form 2 - Lay Summary," a one-page protocol summary form submitted by investigators as of an initial protocol application and given all IRB members to assist in the review summary. The form instructs investigators to limit the summary to the space provided, about one-half of one page.

Please note the following:

(a) When an IRB uses a primary reviewer system for initial review, the primary reviewer(s) should do an in-depth review of all pertinent documentation. All other IRB members should at least receive and review a protocol summary (**of sufficient detail to make the determinations required under HHS regulations at 45 CFR 46.111**), the proposed informed consent document, and any advertising material. In addition, the complete documentation should be available to all members for review.

> (b) For most research protocols undergoing initial review, a half-page summary would generally not be able to provide sufficient detail to make all of the determinations required under HHS regulations at 45 CFR 46.111.

(4) Regarding the boilerplate language for informed consent documents on page 66, OHRP notes the following statement under the section "Voluntary Participation:"

> "Your participation in this project is voluntary and you may withdraw at anytime without prejudice to your future care at the North Shore-Long Island Jewish Health System . . . ."

Please note that HHS regulations at 45 CFR 46.116(a)(8) require that informed consent for research include a statement that participation is voluntary, refusal to participate will involve **no penalty or loss of benefits to which the subject is otherwise entitled**, and the subject may discontinue participation at any time **without penalty or loss of benefits to which the subject is otherwise entitled**.

The above boilerplate statement should be expanded to include a reference to "no penalty or loss of benefits to which the subject is otherwise entitled."

(5) Regarding Section 7.2, Research Involving Fetuses, Pregnant Women, or Human *in vitro* fertilization, please note that a revised Subpart B of 45 CFR Part 46 became effective on December 13, 2001 (see http://ohrp.osophs.dhhs.gov/humansubjects/guidance/45cfr46.htm#subpartb).

(6) Regarding Section 7.4, Research Involving Incapacitated or Decisionally Impaired Subjects, page 97, OHRP notes the following statement:

> "**There are certain circumstances where it may be appropriate to allow next-of-kin, who may not be a Legally Authorized Representative, to provide consent on behalf of an individual. The determination as to whether or not it is appropriate to accept consent by a next-of-kin is considered for individual protocols by the IRB, and is based on the risk/benefit ratio and the implications of delaying study participation for the amount of time it would take to appoint a legal guardian.**"

Please note that HHS regulations at 45 CFR 46.116 stipulate that, except as provided elsewhere in the regulations, no investigator may involve a human being as a subject in research unless the investigator has obtained the legally effective informed consent of the subject or the

subject's legally authorized representative. "Legally authorized representative" is generally determined by applicable state law. The only exceptions to this requirement are as follows:

> (a) The IRB has waived the requirement for informed consent in accordance with the requirements of (i) HHS regulations at 45 CFR 46.116 (c) or (d); (ii) the Food and Drug Administration (FDA) regulations at 21 CFR 50.24 for research regulated by the FDA; or (iii) the HHS Secretary's October 2, 1996 waiver of the applicability of the 45 CFR Part 46 requirements for obtaining and documenting informed consent under HHS regulations at 45 CFR 46.101(i) (see OPRR Reports 97-01 at http://ohrp.osophs.dhhs.gov/humansubjects/guidance/hsdc97-01.htm).
>
> (b) The research involves only one or more of the exempt categories of research stipulated by HHS regulations at 45 CFR 46.101(b).

Section 7.4 of the NSLIJHS IRB Policies and Standard Operating Procedures appears to allow for other exceptions that would not be permissible under the HHS regulations.

(7) Regarding Section 8.1, Emergency Use Exemption from Prospective IRB Approval, page 110, please note that HHS regulations do not permit research activities to be started, even in an emergency, without prior IRB review and approval, although emergency medical care is not precluded by the regulations (see 45 CFR 46.103(b), 46.116(f), OPRR Report 91-01 at http://ohrp.osophs.dhhs.gov/humansubjects/guidance/hsdc91-01.htm, and OPRR Report 97-01). When emergency medical care is initiated without prior IRB review and approval, the patient may not be considered a research subject. When emergency care involves investigational drugs, devices, or biologics, U.S. Food and Drug Administration (FDA) requirements must be satisfied.

(8) Continuing IRB review of research must be substantive and meaningful. In conducting continuing review of research not eligible for expedited review, **all IRB members should at least receive and review** a protocol summary and a status report on the progress of the research, including (a) the number of subjects accrued; (b) a description of any adverse events or unanticipated problems involving risks to subjects or others and of any withdrawal of subjects from the research or complaints about the research; (c) a summary of any recent literature, findings obtained thus far, amendments or modifications to the research since the last review, reports on multi-center trials and any other relevant information, especially information about risks associated with the research; and (d) a copy of the current informed consent document. Primary reviewer systems may be employed, **so long as the full IRB receives the above information**. Primary reviewers should also receive a copy of the complete protocol including any modifications previously approved by the IRB (see OPRR Reports 95-01 at http://ohrp.osophs.dhhs.gov/humansubjects/guidance/hsdc95-01.htm). Furthermore, the

minutes of IRB meetings should document separate deliberations, actions, and votes for each protocol undergoing continuing review by the convened IRB.

OHRP appreciates the continued commitment of your institution to the protection of human research subjects. Please do not hesitate to contact me should you have any questions.

Sincerely,

Michael A. Carome, M.D.
Director, Division of Compliance Oversight

cc: Ms. Jacki Altman, Director, Office of the IRB, NSLIJHS
Dr. Martin L. Lesser, Chair, IRB, NSLIJHS
Commissioner, FDA
Dr. David Lepay, FDA
Dr. James McCormack, FDA
Dr. Greg Koski, OHRP
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